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10/840,182	05/05/2004	Michael D. Cleary	STAN-304	7494

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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/840,182	CLEARY ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7-27,33,34,36 and 37* is/are pending in the application.

4a) Of the above claim(s) *8,9,12,14-17,20-22 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5, 7, 10-11, 13, 18-19, 23, 33-34 and 36-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Amendment filed on September 8, 2008 is acknowledged. Applicant has amended claims 5 and 33; cancelled claims 1-4, 6, 28-32, 35 and 38-41; and withdrawn claims 8-9, 12, 14-17, 20-22, 24-27. Claims 5, 7, 10-11, 13, 18-19, 23, 33-34, 36-37 are currently active and will be examined in this action.

Response to Arguments

Re 102 rejection of claims 33-34 over Shibata et al.

2. Applicant's arguments with respect to claims 33-34 have been considered but are moot in view of the new ground(s) of rejection. Applicant has amended claim 33 to add the limitation of former claim 35. Shibata et al. did not teach the limitation of former claim 35. Accordingly the Shibata et al. do not teach amended claim 33. Accordingly 102 rejection of claims 33-34 over Shibata et al. is no longer valid and is being withdrawn. New grounds of rejection are being presented that address all the limitations of the amended claim 33.

Re 103 rejection of claims 35, 37 over Shibata et al. in view of Al-Anouti et al.

3. Since 102 rejection of base claim 33 over Shibata et al. is withdrawn, accordingly the 103 rejection of claims 35 and 37 over Shibata et al. further in view of secondary reference Al-Anouti et al. are no longer valid. Hence previous rejection of claims 35 and 37 over Shibata et al. in view of Al-Anouti et al. is withdrawn.

Re 103 rejection of claim 36 over Shibata et al. in view of Maddry et al. as evidenced by Chan and evidenced by Diamandis & Christopoulos

4. Since 102 rejection of base claim 33 over Shibata et al. is withdrawn, accordingly the 103 rejection of claim 36 over Shibata et al. further in view of secondary references are no longer valid. Hence previous rejection of claim 36 over Shibata et al. in view of Maddry et al. as evidenced by Chan and evidenced by Diamandis & Christopoulos is withdrawn.

Re 103 rejection of claims 5, 7, 10-11, 13, 18-19 over Melvin et al. and Rana as evidenced by Diamandis and Christopoulos

5. Applicant's arguments with respect to claims 5, 7, 10-11, 13, 18-19 have been considered but are moot in view of the new ground(s) of rejection. Applicant has amended claim 5 in two ways:

1) Added the limitation---" and wherein said uracil analog is not the corresponding uracil-containing nucleoside and said phosphoribosyl transferase is exogenous to said cell"--; Melvin et al. label the RNA using 4-TU (4 – thiouridine) which is uracil-containing nucleoside. This uracil-containing nucleoside is specifically excluded from the current claim recitation.

2) Deleted ---"nucleoside kinase"-- from the claim recitation. Mammalian cells lack UPRT but the cells do contain various other phosphoribosyl transferases however all these phosphoribosyl transferases are endogenous to said cell.

Thus Melvin et al. do not teach the newly added limitations and wherein said uracil analog is not the corresponding uracil-containing nucleoside and said phosphoribosyl transferase is exogenous to said cell;.

Accordingly, 103 rejection of claims 5, 7, 10-11, 13, 18-19 over Melvin et al. and Rana as evidenced by Diamandis and Christopoulos is no longer valid and is being withdrawn. New grounds of rejection are being presented that address the two aspects of the newly added limitations:

1) the phosphoribosyl transferases that are exogenous to the cell

2) uracil analog is not the corresponding uracil-containing nucleoside or in other words it is just the nucleobase uracil.

Re 103 rejection of claim 23 over Melvin et al. and Rana as evidenced by Diamandis and Christopoulos as applied to claim 5 above further in view of Tiraby et al.

6. Since 103 rejection of claim 5 over Melvin et al. and Rana as evidenced by Diamandis and Christopoulos is no longer valid, accordingly the rejection of claim 23 further in view of secondary reference Tiraby et al. is not valid and is being withdrawn.

Claim interpretation

7. Applicant has not provided any specific definition of "tag" or "conjugating" in the specification. Examiner is interpreting "tag" to mean any means that may be used to bind RNA through said thiol moiety. "Conjugating" is being broadly interpreted as any mechanism by which the thiol moiety can be bound to the "tag". This binding mechanism includes both, covalent or non-covalent binding.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 5, 7, 10, 18-19 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyers et al. (US PG Pub. 2002/0019030 A1 with filing date of February 27, 2001) as evidenced by Diamandis and Christopoulos (1991) Clin Chem 37 (5) pp 625-636 (provided by Applicant in IDS).

Regarding claim 5, Meyers et al. teach a method comprising:

contacting said cell (see page 3 par. 0035 where culturing host cell in suitable media is taught---thus teaching contacting said cell)

with a uracil analog having a thiol moiety not normally present in RNA (see page 16 par. 0159 where 5-methoxyaminomethyl-2-thiouracil, 5 methyl-2-thiouracil, 2-thiouracil, and 4-thiouracil are taught. Thus, teaching uracil analogs having a thiol moiety not normally present in RNA).

In view of above combined teachings, by teaching culturing host cell in suitable media Meyers et al. teach contacting said cell with a uracil analog having a thiol moiety not normally present in RNA),

wherein said cell comprises a phosphoribosyltransferase operably linked to a promoter that can be activated in said cell; (see page 3 par. 0035 where host cell containing a recombinant expression vector is taught, by teaching a

recombinant expression vector (see page 22 par. 0203) Meyers et al. teach cell comprises a gene of interest operably linked to a promoter that can be activated in said cell. They also teach in same par. a recombinant expression vector comprising a transferase nucleic acid. Thus Meyers et al. teach cell comprises a transferase operably linked to a promoter that can be activated in said cell. See page 2 par. 0022 where phosphoribosyltransferases (PRT) are taught. Thus teaching wherein said cell comprises a phosphoribosyltransferase operably linked to a promoter that can be activated in said cell (see page 23 par. 0206 where inducible promoters are taught thus teaching a promoter that can be activated in said cell),

and that can specifically incorporate said uracil analog into the corresponding nucleotide (see page 2, par. 0022 where PRT's involved in biosynthesis of purine, pyrimidine and pyridine nucleotides and salvage of purines and pyrimidines are taught. Thus teaching a phosphoribosyltransferase operably linked to a promoter that can be activated in said cell and that can specifically incorporate said uracil analog (—a pyrimidine) into the corresponding nucleotide,

and said phosphoribosyl transferase is exogenous to said cell (by teaching culturing of transformed host cell with recombinant phosphoribosyltransferase expression vector, Meyers et al. teach said phosphoribosyl transferase is exogenous to said cell;

and wherein said uracil analog is not the corresponding uracil-containing nucleoside (see page 16 par. 0159 where 5-methoxyaminomethyl-2-thiouracil, 5

methyl-2-thiouracil, 2-thiouracil, and 4-thiouracil are taught. All these uracil analogs meet the limitation namely wherein said uracil analog is not the corresponding uracil-containing nucleoside)

obtaining RNA comprising said thiol moiety from said cell (see page 36 par. 0319 where isolated RNA is taught. Thus teaching obtaining RNA from said cell. Since the cells were cultured in presence of the thiol containing uracil, the RNA made from those cells will have the RNA comprising said thiol moiety;

and conjugating a small molecule binding partner to said thiol moiety (see page 37 par. 0325 second last line where biotin is taught as a label. By teaching biotin as a label, Meyers et al. teach conjugating a small molecule binding partner to said thiol moiety.

The thiol moiety in the RNA can be used to bind biotin molecule is evidenced by teachings of Diamandis and Christopoulos (1991) where on page 630 last par. they teach ---- 4 thiouridine containing nucleic acid is taught to be biotinylated by using haloacetamido derivative of biotin e.g. iodoacetyl-LC-biotin that reacts with thiol group on the nucleic acid to result in biotinylated nucleic acid. See page 629 par. 4 where they state "Another useful class of biotinylated nucleotides consists of nucleotides that contain S-S within the structure of the linker arm. These "releasable" nucleotide analogs can be used in applications where the nucleic acid needs to be released after it's binding to streptavidin".

Thus Meyers et al. anticipate the claimed method of biosynthetically labeling RNA in a cell of interest as recited in claim 5.

Regarding claim 7, Meyers et al. teach wherein said small molecule binding partner is biotin. (see page 37 par. 0325 second last line where biotin is taught).

Regarding claim 10, Meyers et al. teach method further comprising the step of binding a specific binding partner to said small molecule binding partner. (see page 37 par. 0325 last two lines where detection of biotin using fluorescently labeled streptavidin is taught. Thus teaching step of binding a specific binding partner (streptavidin) to said small molecule binding partner (biotin).

Regarding claim 18, Meyers et al. teach wherein said specific binding partner is conjugated to a detectable label. (see page 37 par. 0325 where fluorescently lableled specific binding partner –namely fluorescently lableled streptavidin is taught. Thus teaching said specific binding partner is conjugated to a detectable label)

Regarding claim 19, Meyers et al. teach wherein said detectable label is a fluorochrome, radiolabel, heavy metal label, or enzyme conjugate. (see page 17 par. 0168 where fluorescent, radioactive or calorimetric labels are taught. Thus teaching wherein said detectable label is a fluorochrome, radiolabel).

Regarding claim 23, Meyers et al. teach wherein said promoter is constitutively active in said cell of interest (see page 23 par. 0206 where constitutive promoter is taught. Thus teaching wherein said promoter is constitutively active in said cell of interest).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 11 and 13 are rejected under 35 U.S.C. . 103(a) as being unpatentable over Meyers et al. as evidenced by Diamandis & Christopoulos as applied to claim 10 above in view of Rana (P.G. Pub 2004/0175732 filed on November 17, 2003 with a priority date of November 15, 2002)

Regarding claim 11, Meyers et al. as evidenced by Diamandis & Christopoulos teach method of claim 10 but do not teach wherein said specific binding partner is conjugated to an insoluble substrate for affinity

chromatography, and wherein said biosynthetically labeled RNA is separated from non-labeled RNA.

Regarding claim 11, Rana teaches wherein said specific binding partner is conjugated to an insoluble substrate for affinity chromatography, and wherein said biosynthetically labeled RNA is separated from non-labeled RNA. (see page 6, par. 0065 where use of streptavidin coated beads to separate biotin labeled RNA from total RNA is taught. Here specific binding partner (streptavidin) is conjugated to an insoluble substrate (beads) for affinity chromatography, and wherein said biosynthetically labeled RNA is separated from non-labeled RNA.

Regarding claim 13, Rana teaches wherein said separated RNA is amplified. (see page 6, par. 0069 where amplification of RNA by reverse transcription is taught).

Regarding claim 18, Rana teaches wherein said specific binding partner is conjugated to a detectable label. (see page 13, par. 0145 where avidin and streptavidin conjugated to different detectable labels magnetic particles, superparamagnetic microspheres are taught. Further Rana teaches custom synthesis of beads when biotin/avidin or biotin/streptavidin system is used. Thereby Rana teaches the specific binding partner could be labeled with any other desired detectable label).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Rana in the method of labeling RNA taught by Meyers et al. as evidenced by Diamandis & Christopoulos.

The motivation to do so is provided to one of ordinary skill by teaching of both Diamandis & Christopoulos and Rana.

Meyers et al. teach a method of labeling RNA with thiol groups. This thiolated RNA can be further biotinylated and the biotinylated RNA can be separated from non tagged RNA using the techniques taught by Rana.

Rana states " -----biotinylated miRNAs can be made incorporating 4-thio uridine or thymidine or 6-thio guanosine in the miRNA sequence, as illustrated in ---.The 4-thio uridine, 4-thio thymidine or 6-thio guaosine can be incorporated into the RNA sequence of the miRNA according to methods known in the art e.g. as described in --------. Total mRNA is isolated from the cell and streptavidin coated beads added to the extract to enrich for the miRNA target complexes---- (see page 6 par. 0065).

Thus Rana explicitly teaches one of ordinary skill that thiolated RNA produced by incorporation of 4-thio or 6-thio precursors are substrate to which biotin tag can be conjugated. Once thiolated RNA is tagged with biotin now the streptavidin chemistry can be exploited for detection of various downstream products resulting from use of labeled RNA.

Based on teachings of Diamandis and Christopoulos on page 630 last par. where they teach ---- biotinylation of thiol containing nucleic acid by using haloacetamido derivative of biotin e.g. iodoacetyl-LC-biotin that reacts with thiol group on the nucleic acid to result in biotinylated nucleic acid. See page 629 par. 4 where they state "Another useful class of biotinylated nucleotides consists of nucleotides that contain S-S within the structure of the linker arm. These

"releasable" nucleotide analogs can be used in applications where the nucleic acid needs to be released after its binding to streptavidin". Thus one of ordinary skill knows that thiolated RNA bound to streptavidin can be released after binding to streptavidin.

So if the specific binding partner (streptavidin) is conjugated to an insoluble substrate (beads) for affinity chromatography, one of ordinary skill recognizes the ease with which the thiol containing RNA can be purified using an affinity matrix coated with streptavidin. Only the biotin labeled RNA would bind to streptavidin while all other RNA not containing biotin label can be washed off. Then the thiol labeled RNA can be released from the affinity matrix coated with streptavidin by simply using an elution solution containing appropriate amount of DTT thereby the final product can be released using dithiothreitol based cleavage or elution.

13. Claims 33-34 and 37 are rejected under 35 U.S.C. . 103(a) as being unpatentable over Meyers et al. (US PG Pub. 2002/0019030 A1 with filing date of February 27, 2001) in view of Al-Anouti et al. (January 2003) Biochemical and Biophysical Research Communications vol. 302: pp. 316-323—Previously provided to applicant).

Regarding claim 33, Meyers et al. teaches a method comprising:

contacting said cell (see page 3 par. 0035 where culturing host cell in suitable media is taught---thus teaching contacting said cell)

with a uracil analog having a reactive thiol moiety not normally present in RNA (see page 16 par. 0159 where 5-methoxyaminomethyl-2-thiouracil, 5

methyl-2-thiouracil, 2-thiouracil, and 4-thiouracil are taught. Thus, teaching uracil analogs having a reactive thiol moiety not normally present in RNA).

In view of above combined teachings, by teaching culturing host cell in suitable media Meyers et al. teach contacting said cell with a uracil analog having a reactive thiol moiety not normally present in RNA,

and wherein said uracil analog is not the corresponding uracil-containing nucleoside (see page 16 par. 0159 where 5-methoxyaminomethyl-2-thiouracil, 5 methyl-2-thiouracil, 2-thiouracil, and 4-thiouracil are taught. All these uracil analogs meet the limitation namely wherein said uracil analog is not the corresponding uracil-containing nucleoside),

by teaching culturing of transformed host cell with recombinant phosphoribosyltransferase expression vector, Meyers et al. teach said phosphoribosyl transferase is exogenous to said cell;

(See Meyers et al. page 2, par. 0022 where PRT's involved in biosynthesis of purine, pyrimidine and pyridine nucleotides and salvage of purines and pyrimidines are taught). Thus teaching a phosphoribosyltransferase that can convert said uracil analog (—a pyrimidine) into the corresponding nucleotide namely uridine monophosphate,

wherein said uracil analog is incorporated into RNA synthesized by said cell (since the cells were cultured in presence of the thiol containing uracil, and uracil is a component of RNA, therefore RNA made from these cultured cells will necessarily meet the limitation that said uracil analog is incorporated into RNA synthesized by said cell).

Regarding claim 34, Meyers et al. teach wherein sequences encoding said desired phosphoribosyltransferse are operably linked to a promoter that is active or can be activated in said cell (see page 23 par. 0206 where both constitutive and inducible promoters are taught. Thus teaching wherein sequences encoding said desired phosphoribosyltransferse are operably linked to a promoter that is active or can be activated in said cell)

Regarding claim 33, Meyers et al. do not specifically recite wherein said phosphoribosyltransferase is uracil phosphoribosyltransferase (UPRT) that can convert said uracil analog to the corresponding uridine monophosphate

Regarding claim 33, Al-Anouti et al. teaches wherein said phosphoribosyltransferase is uracil phosphoribosyltransferase (UPRT) (see page 317, par. 4 where pUC19UPRT plasmid is taught. The phosphoribosyltransferase gene in this plasmid is uracil phosphoribosyltransferase (UPRT).

Regarding claim 37, Al-Anouti et al. teaches wherein said UPRT is Toxoplasma gondii UPRT or a functional derivative thereof (see page 316 title and abstract where *Toxoplasma gondii* uracil phosphoribosyltransferase (TgUPRT) is taught) .

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to clone the uracil phosphoribosyltransferase (UPRT) gene from the pUC19UPRT plasmid taught by Al Anouti et al. into the expression vector taught by Meyers et al.

The motivation to do so is provided to one of ordinary skill by the teaching of Meyers et al. who teach expression systems for expressing various

phosphoribosyltransferases in various host cells. Al Anouti teaches the sequence of cloned UPRT gene in pUC19 shuttle vector. Hence one of ordinary skill can easily cut the cloned UPRT gene out of pUC19 vector and clone it into the expression system taught by Meyers et al. One of ordinary skill in the art would have had a reasonable expectation of success that this UPRT containing expression system created by them can be introduced into the various host cells (as taught by Meyers et al.) such that now RNA made from any of these transformed cells can be readily labeled by growing the cells in presence of thiolated uracil precursors. Thus allowing one of ordinary skill in the art an easy, non toxic, rapid and reliable method of incorporating thiol moieties into RNA synthesized in a cell by simply growing the cell culture in presence of thiol containing uracil precursors.

14. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meyers et al. (US PG Pub. 2002/0019030 A1 with filing date of February 27, 2001) in view of Al-Anouti et al. (January 2003) Biochemical and Biophysical Research Communications vol. 302: pp. 316-323—previously provided to applicant) as applied to claim 33 above further in view Maddry et al. (US pat. 5,561,225 Oct 1, 1996) and Shibata et al. (1982) Plant and Cell Physiol. Vol. 23(3) : 365-374 as evidenced by Chan (US Pat. 6,403,311 B1 filed Aug 13, 1999) and evidenced by Diamandis and Christopoulos (1991) Clin Chem 37 (5) pp 625-636 (provided by Applicant in IDS).

Regarding claim 36, Meyers et al. and Al-Anouti et al. teach method of claim 33, but do not teach uracil analog 2, 4 dithiouracil.

Regarding claim 36, Maddry et al. teach 2, 4- dithiouracil as a uracil analog (see col. 4 line 3) along with a whole series of purine and pyrimidine analogs, which contain sulfonate and sulfonamide linkages.

Regarding 2, 4- dithiouracil one of ordinary skill in the art is taught by art that it is an analog that has the characteristic energy emission pattern of a light emitting compound (as evidenced by Chan US pat. 6,403,311 B1 issued Jun 11, 2002 . See col. 11 lines 32-42)

It would have been prima facie obvious to one of ordinary skill in the art to use uracil analog 2,4 dithiouracil out of the numerous analogs taught by Maddry et al. in the method of Meyers et al. and Al-Anouti et al. at the time the invention was made.

The motivation to do so is provided to one of ordinary skill in the art by both the art itself as well as Shibata et al.

Shibata et al. state "since 4 SU-derivatives (4-thio-U) have maximum absorptions near 330 nm, as compared to the maxima near 260nm of typical nucleic acid components, the presence of 4SU- metabolites can be monitored by their characteristic absorptions. But, water soluble flavonoids -----interfere with the measurements of 4SU-metabolites. Recently we reported an Hg-cellulose affinity chromatography for 4SU-containing RNA" (see page 368 par. 1). Thus using 4 thio uracil one is able to affinity purify labeled RNA.

Having an additional thio molecule in 4 thio Uracil would result in RNA being labeled with S-S bond. While one thio group is used to bind to Hg-cellulose affinity column. The presence of S-S bond would allow cleavage by DTT hence

easy elution of labeled RNA. Diamandis and Christopoulos state " another useful class of biotinylated nucleotides consists of nucleotides that contain S-S within the structure of the linker arm. These "releasable" nucleotide analogs can be used in applications where the nucleic acid needs to be released after binding to streptavidin" (see page 630 last par).

One of ordinary skill would have had a reasonable expectation of success for labeling RNA using 2, 4-dithiouracil as a substrate that when fed to the cells containing UPRTase will be taken up and incorporated into newly synthesized RNA. This is because Shibata et al. show labeling of 4 thio Uracil at position 2 with C^{14} does not interfere with its uptake or incorporation into RNA. So 2,4-dithiouracil should be taken up. Such a labeled RNA will have triple advantages namely: one can use affinity purification; use the S-S bond to bind biotin; and also have a characteristic energy emission pattern of a light emitting compound.

Conclusion

15. All claims under consideration 5, 7, 10-11, 13, 18-19, 23, 33-34, 36-27 are rejected.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is

filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

Suchira Pande
Examiner
Art Unit 1637